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HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
SPECTOR, LORRAINE	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/902,615
Filing Date: July 10 2001
Appellant(s): ASHKENAZI ET AL.

Ginger Dreger
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5/16/2006 appealing from the Office action mailed 2/4/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

In addition to the antibody and nucleic acid applications disclosed by Appellants, the Examiner notes that there are a multitude of applications that are also in prosecution or under appeal that are drawn to different protein or nucleic acid sequence, but involve the same issues on appeal, namely the skin vascular permeability assay, with regard to 35 U.S.C. §101 and §112, first paragraph.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is largely correct. The art rejections are withdrawn herein as they applied to claims 40 and 41, but maintained against claims 39 and 43.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Monks et al., Journal of the National Cancer Institute, vol. 83(11):757-766

Johnson et al. (Brit. J. Cancer 84(10):1424-1431)

Shi et al., (J. Chem. Inf. Comput. Sci. 40:367-379)

Senger et al. (1983, Science 219:983-985)

Rampart et al. (Am. J. Pathol. 135:21, 1989)

Hirahara et al. (1993, Thrombosis Res. 71:139-148)

Yeo et al. (1992, Clin. Chem. 38:71-75)

KAWAI, Locus A9D332, 6/1/01

NAGASE, Locus O94898, 5/1/99

SUZUKI, Locus P70193, 2/1/97

6,046,030	Wu et al.	12/97
6,426,072	WANG	8/00
5,783,187	GROTENDORST	7/98
WO94/01548	SIBSON	1994

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 39-41 and 43 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

The specification discloses a protein designated PRO326, and nucleic acid encoding such. At page 31 of the specification it is disclosed that PRO326 has (unspecified) homology to members of the leucine rich repeat superfamily. At page 110 it is stated that PRO335, 331 and 326 polypeptides "are related to LIG-1 and possess the biological functions of this family." However, what specific biological functions PRO326 possesses that are in common with LIG-1, and what uses that would indicate for PRO326 are not indicated. At page 138, it is stated "Uses for PRO335, PRO331 or PRO326 including uses in competitive assays with LIG-1, ALS and decorin *to determine their relative activities* (emphasis added)." Because there are no utilities asserted for the claimed antibodies, the implicit utility therefore is to assay or isolate the protein to which the antibodies bind. Accordingly, to have utility, the protein to which the antibodies bind must also have utility, that is, the utility of the antibodies flows from that of the protein.

Utility must be in readily available form. In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct,.1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to a protein which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the protein identified in the specification as PRO326 protein, the claimed invention is incomplete. Merely using the protein to determine the properties thereof does not constitute a patentable utility.

It is further noted that PRO326 is disclosed as having given positive results in three assays. The first is found at pages 208-209 of the specification, and is described as a mixed lymphocyte reaction. The specification states that "any value greater than control indicates a stimulatory effect for the test protein." This assay is not considered to impart utility to the protein PRO326, nor to the nucleic acids that encode it. The reason for this determination is that no results are presented, and the standard disclosed, "any value greater than control", is not

considered to be an acceptable standard in the scientific community. It is well accepted in experimental science that, in order for a result to be positive, it must be *significantly* different from the control value, not "any value greater" as reported in the specification. Accordingly, the tacit assertion that PRO326 has a positive reaction in a mixed lymphocyte assay, and could therefore be used 'as a stimulator of the proliferation of stimulated T-lymphocytes" does not meet the requirements of 35 U.S.C. § 101, as the assertion of utility would not be considered substantial by a person of ordinary skill in the art.

The second assay in which PRO326 was stated to give positive results is found at pages 210-211, the skin vascular permeability assay (Assay 64). Presumably a positive reaction indicates that a measurable blemish was observed (though this is not clearly stated), and then biopsied, and one or more types of inflammatory cells were observed in the biopsy. This assay is not considered to be indicative of utility for PRO326, because it is merely what is commonly known as an immediate type hypersensitivity assay, and does not inform as to what the protein could be used for, especially in the absence of any information as to what *particular* cell types were observed in the biopsy. Thus, it is not clear what type of immune response was stimulated, nor what utility would stem from such. Again, the person of ordinary skill in the art would not find that this assay constitutes a specific, substantial and credible assertion of utility.

Finally, at pages 218-222 (Example 91), the specification discloses an in vitro antitumor assay (assay 161). The specification discloses, in Example 91, that the PRO326 protein was active, causing at least 50% growth inhibition, against four of the 60 cell lines of the National Cancer Institute (NCI) anticancer drug discovery screen (the NCI panel). The asserted utility of nucleic acids encoding the PRO326 protein as a possible chemotherapeutic agent is not considered to be specific, substantial and credible, for the following reasons: Monks et al., Journal of the National Cancer Institute, vol. 83(11):757-766, cited by applicants at page 218, disclose and explain the screen itself, including how the screen is performed, and what cell lines are used. The 60 cell lines are independent isolates representing seven distinct types of cancer, namely lung cancer (13 cell lines), renal cancer (9 cell lines), colon cancer (9 cell lines), melanoma (9 cell lines), CNS cancer (8 cell lines), ovarian cancer (6 cell lines), and leukemia (6 cell lines). The specification, at pages 218-222, discloses that PRO326 tested positive in 4 cell lines, representing three CNS, and one NSCL cancers. Based on disclosed results for other PRO

polypeptides, other cell lines tested included a variety of cancer cell lines, including breast cancer cell lines. As the Monks et al. disclosure does not disclose any breast cancer cell lines as being in the panel, it is not clear exactly *which* "NCI panel" was used.. It is also noted that the composition of the NCI panel is not static, as Shi et al., referenced below, disclose a different set of 60 cell lines than that disclosed by Monks et al. It cannot be determined how many CNS and NCSL cancer cell lines were present in the panel used. Therefore, there is no discernable pattern of activity, i.e. the protein does not appear to be active against any particular type of cancer, nor against anything approaching a majority of the cell lines for any given type of cancer. Since PRO326 does not appear to give significant results when tested against the NCI panel, the implicit assertion of utility for the protein (and by extension nucleic acids encoding such) as an anti-cancer agent is not specific, as such could be asserted for almost any protein, which would be toxic for one or more cell types at some concentration. Further, the implicit assertion of anticancer activity is not substantial. Johnson et al. (Brit. J. Cancer 84(10):1424-1431), in an article entitled "Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials", state, with regard to the NCI panel that "Agents selected on the basis of potency, selective activity against a particular disease category, and/or differential activity against a few specific cell lines were then evaluated against a small number of sensitive human tumours in the nude mouse xenograft model (citations omitted) as a basis for selecting compounds for further preclinical development. Owing to the large numbers of molecules emerging from the in vitro screen as candidates for xenograft testing, in 1995 this development path was further modified to include a hollow fibre (HF) assay, activity in which was a prerequisite for study in classical xenograft models" (page 1424, second column). Thus, the initial screen against the 60 cell lines of the NCI panel is not considered by the art to be predictive of *in vivo* activity against tumors, and, as characterized by Johnson et al., such is merely the first of a three-part protocol for identification of agents to be tested in vivo. Further, Shi et al., (J. Chem. Inf. Comput. Sci. 40:367-379), clearly state that "Although cell growth inhibitory activity for a *single* cell line is not very informative, activity *patterns* across the 60 cell lines can provide incisive information on the mechanisms of action of screened compounds...." (abstract). The paper, drawn to methods of mining and visualizing the large amounts of data generated by the NCI panel, further states that relative activity levels distinguish better among

the tested cell lines than do the GI_{50} activity patterns, and that "The mean zero preprocessing procedure seemed to eliminate the noninformative "inherent" cytotoxicity, thus brining out the informational differential cell responses (p. 377, end of first column). Thus, Shi et al. indicates that the art does not consider the raw GI_{50} data are insufficient to identify compounds that are likely to be antitumor candidates to be tested further. Accordingly, the implicit assertion of utility as an anti-cancer agent is not substantial, as the art does not support that mere identification of 50% killing of 4 of the 60 NCI panel cell lines would be predictive of anti-tumor activity, and thus would not constitute a substantial and credible utility for PRO326 and by extension nucleic acids encoding such.

In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to antibodies that bind a protein which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the protein identified in the specification as PRO326 protein or the polynucleotides encoding it, the claimed invention is incomplete.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-41 and 43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Rejections Over Prior Art

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 39 and 43 remain rejected under 35 U.S.C. 102(e) as being anticipated by Wu et al., U.S. Patent Number 6,046,030.

U.S. Patent Number 6,046,030 teaches a protein of SEQ ID NO: 5, having 50% identity to residues 1-1083 of SEQ ID NO: 294, and SEQ ID NO: 2, having 49.8% identity to residues 32-1036 of SEQ ID NO: 294. 21 lines 59 to column 22 line 17. Labeled antibodies are disclosed at column 23, lines 42-53. Because of the relatedness of Wu's sequences to those of SEQ ID NO: 294, Wu's antibodies would reasonably be expected to meet the limitations of the rejected claims. Applicants argument that the antibodies of Wu would not be considered to specifically bind to the protein of SEQ ID NO: 294 has been fully considered but is not deemed persuasive. As used in the art, 'specific' is not necessarily synonymous with 'binds exclusively

to' as urged by applicants. Rather, specificity is relative, such that antibodies 'specific' for one protein can bind to another protein with similar sequence. For example, antibodies specific to PDGF have, indeed, been described as binding to CTGF, as evidenced by U.S. Patent Number 5,783,187. Accordingly, antibodies to Wu's protein that also bind to the same epitopic structure of SEQ ID NO: 294 would be considered to be "specific", and the antibodies of Wu anticipate the claims.

Claims 39 and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Wang et al., U.S. Patent Number 6,426,072.

U.S. Patent Number 6,426,072 teaches SEQ ID NO: 4, which has 74.8% identity to residues 608-737 of SEQ ID NO: 294.

Antibodies to the proteins, including single chain and humanized antibodies, are disclosed at column 50. Immunoassays using labeled antibodies are disclosed at col. 25. Because of the relatedness of Wang's sequences to those of SEQ ID NO: 294, Wang's antibodies would reasonably be expected to meet the limitations of the rejected claims. Applicants argument that Wang is not applicable as prior art is deemed not persuasive for reasons of record regarding the priority date of this application.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A search of the protein sequence databases revealed the following prior art:

Locus	Date	Author	Identity to SEQ ID NO:294
Q9D332	6/1/01	J. Kawai et al.	86% to residues 378-1119
O94898	5/1/99	T. Nagase et al.	58.4% to residues 47-1036
P70193	2/1/97	Y. Suzuki et al.	50% to residues 1-1083

Claims 39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawai et al. or Nagase et al. or Suzuki et al., any of the three in view of in view of Sibson et al., WO94/01548.

The three primary references disclose proteins with varying amounts of identity to SEQ ID NO: 294, as summarized above. Each is disclosed as being encoded by an isolated cDNA. The primary references do not specifically disclose production of antibodies to the proteins.

Sibson et al. disclose that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such cDNA's. See pages 8-13. Sibson teaches the use of such antibodies to detect proteins to which they bind, which would indicate labeling of the antibodies.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made make antibodies to any of the proteins disclosed by Kawai et al. or Nagase et al. or Suzuki et al. as taught by Sibson et al. in view of Sibson et al.'s suggestion that it would be desirable to do so, as cited above. The production of polyclonal, chimeric, single chain, and labeled antibodies, as well as of hybridoma cells that produce antibodies is further considered obvious over Kawai et al. or Nagase et al. or Suzuki et al. in view of Sibson et al., as all are notoriously old and well known in the art, and would be immediately envisaged by the person of ordinary skill in the art upon reading the Sibson et al. disclosure.

(10) Response to Argument

It is noted that appellants have, throughout prosecution, chosen to argue only one of the grounds for finding lack of utility above, namely the vascular permeability assay. The discussion of the other two assays in the grounds of rejection is included above in the interest of presenting to the Board a complete and accurate representation of the prosecution in this application.

At pages 4-8 of the Brief, appellants present an overview of their arguments. As the overview is redundant of the "detailed arguments" beginning at page 8, the Examiner will address the former in the context of the latter only (i.e. all arguments will be addressed with respect to the 'detailed arguments' section. The gist of the arguments is that the vascular permeability assay shows that the polypeptide to which the claimed antibodies bind is a proinflammatory molecule, and that the protein is thus useful to induce inflammation (page 4, last full paragraph), "useful as proinflammatory agents, where inflammation to enhance or induce an immune response is desired" and that the claimed antibodies will thus inhibit inflammation. The Examiners position, in brief, is that the assay in question is *not*, by itself, accepted in the art as establishing that it is more likely than not that a compound is a proinflammatory molecule, rather all it establishes is that the molecule is toxic or irritating, and that substantial further experimentation, of the type found to be part of the invention itself, would be required to determine how to use the protein, and hence the claimed antibodies. Further, even *if* the protein could be used to induce inflammation, it is not predictable that inflammation is caused *in vivo* by PRO326, which finding would be requisite in order to predict whether or not the claimed antibodies could be used to inhibit said inflammation. Simply put, even if PRO326 causes inflammation, that finding does not furnish a nexus between naturally occurring inflammation and PRO326.

At pages 8-12 of the Brief, appellants present a discourse on 35 U.S.C. §101 and applicable case law. The Examiner takes no issue with the discussion, and finds that no response is necessary.

At page 13, appellants assert that the Examiner's finding of lack of utility is unfounded, as *in vitro* and *in vivo* results "are acceptable to demonstrate utility". This argument has been fully considered but is not deemed persuasive. The issue here is not whether generic *in vitro* and *in vivo* results are acceptable to demonstrate utility. The issue here is far more specific; While particular irritants may have uses that stem from that irritant capability, in the absence of further characterization of what type of reaction the substance causes and what the systemic effects of such are, the result remains a preliminary one, necessitating substantial further research to determine an actual, real-world use for the compound. For example, the Rampart reference (Am. J. Pathol. 135:21, 1989), originally cited by appellants, is one in which IL-8 was found to induce plasma leakage and neutrophil accumulation in rabbit skin (title). Rampart et al. did not merely assay the types of cells attracted, but also looked at the kinetics of the reaction, and concluded that based upon the *kinetics* of the responses, which were similar to those induced by C5a and FMLP, that "IL-8, if produced endogenously, may be involved in the acute phase of an inflammatory response to a microbial stimulus". Such is a speculative conclusion, and clearly would indicate to the person of ordinary skill in the art that the authors envisioned that substantial further work would have been required to confirm that speculation. Further, the kinetics of the response have not been investigated for PRO326. In this specific case, human PRO326 was found to be an irritant to guinea pigs. There has been no characterization of the cellular response that was stimulated, nor any characterization of any proinflammatory cytokines that might be stimulated, and finally, there is no nexus between the PRO326 polypeptide and any biological response in the sense that PRO326 has not been shown to be produced *in vivo* as part of an inflammatory or any other kind of response to any stimulus. While the VPF assay *might* indicate that PRO326 is an inflammatory cytokine (although based on such a result, the person of ordinary skill in the art would not consider that to be a supportable conclusion), it might alternatively indicate that the guinea pigs are allergic to PRO326, e.g. that the human PRO326 protein has an epitope that the guinea pigs were pre-sensitized to, or even just that it is an irritant, similar to lye (which would give a similar response in the assay). In either case, as was the case in the Rampart et al. publication, the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of PRO326. Accordingly, Applicants arguments are not persuasive. It remains that the skin vascular permeability assay does not give

sufficient information so as to inform one of skill in the art as to what utility the protein that binds to the claimed antibodies might have, nor how to use such. Further, the Rampart reference is clear evidence of the state of the art, e.g. what one of skill in the art would consider necessary to establish the type of activity (proinflammatory cytokine) urged by appellants.

The Examiner has relied upon the Rampart reference cited by appellants to show the state of the art, and that the skilled artisan would *not* use PRO326 as a pro-inflammatory agent based upon the results in the specification. Appellants have failed to rebut by showing that the skilled artisan *would* use a molecule as they urge based upon such results. With respect to using antibodies to PRO326 as anti-inflammatory agents, such is merely speculative in the express absence of any showing that PRO326 is made as part of an *in vivo* inflammatory response. No such showing has been made.

At page 14, applicants argue that because the PRO326 protein was buffered to pH 6.8, that the observed result cannot be due to pH, i.e. that PRO326 is neither "lye or acid". This argument has been fully considered but is not deemed persuasive because the Examiner has not asserted any mechanism to cause PRO326 to be an irritant, nor has there been an assertion that it is lye or acid. Rather, lye and acid were cited as extreme examples of compositions that would cause the same result observed for PRO326; the point is that the observed result does *not* support the conjectural conclusion that PRO326 is a proinflammatory cytokine. All that has been established by the VPF assay is that the protein was irritating to guinea pigs. While this would be consistent with an eventual finding that PRO326 is a proinflammatory cytokine, it would not be considered by one of ordinary skill in the art to be sufficiently supportive of such speculation. Appellants assertion that PRO326 is not an irritant is not supported by the record. Appellant appears to interpret "irritant" as meaning something of a pH that would cause irritation. No support for that narrow definition is found in the specification, nor in the common use of the term "irritant". An irritant is something that causes irritation. When PRO326 polypeptide was injected under the skin of guinea pigs, it caused irritation. Therefore, it is an irritant. Appellants argue that the examiner's concerns that lye or acid would test positive in the assay are unfounded, since the assay uses a buffered pH of about 6.8. Appellants refer to point 6 of the Fong declaration, as well as pp. 186-188 as providing buffered PRO polypeptide samples. Appellants conclude that the PRO polypeptides are not basic irritants in that they are buffered to be neutral.

This has been fully considered but is not found to be persuasive. The SVP assay at pp. 210-211 of the specification does not indicate that a buffer system was used. Pages 186-188 of the specification do not mention buffers. Therefore, Appellants' argument is without support. Furthermore, pH-neutral irritants would also test positive in this assay. For example, poison ivy extract, splinters, rusty nails, insect saliva, thorns, spider/snake/bee sting venom, etc., all would test positive in the assay. Nevertheless, such substances are not considered to be therapeutically beneficial as pro-inflammatory agents.

Appellants repeatedly argue that the Examiner has failed to cite evidence to support the finding of lack of utility. Specific evidence that PRO326 polypeptide is *not* a proinflammatory molecule is neither required nor possible, as the Examiner does not possess laboratory facilities. As set forth in the MPEP, a finding of lack of utility may be properly made if there is a scientific basis to doubt the assertion of utility. MPEP 2107 (II)(c) clearly states:

> Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence regardless of publication date (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the prima facie showing of no specific and substantial credible utility. If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.

In the instant case, the initial rejection addressed three assays that were disclosed in the specification as supporting asserted utility, and found them all lacking, based on sound scientific reasoning. In response, appellants have chosen, as is their prerogative, to center the prosecution on one of those three, the vascular permeability assay. The Examiner concluded in the first office action on the merits, based upon sound scientific reasoning, that the results of that assay fell far short of supporting the assertion that PRO326 polypeptide is a proinflammatory molecule as a substantial assertion as defined by the Utility Guidelines. Rather, it is a speculative assertion that is a jumping off point for further experimentation to determine the properties of the PRO326 polypeptide.

MPEP2107.01(B) sets forth the definition of a "substantial" utility, to whit:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world"

context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further researchto identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

(A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;

(B) A method of treating an unspecified disease or condition;

(C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility;

(D) A method of making a material that itself has no specific, substantial, and credible utility; and

(E) A claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility.

Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

Appellants assert that PRO326 has a "real world use" as an inflammatory molecule, or that inhibition of PRO326 using the claimed antibody has utility as an anti-inflammatory. The Examiner, supported by the Rampart reference and Miles assay, has concluded that the person of ordinary skill in the art would *not* administer PRO326 or antibodies thereto to a patient for

any reason, including to cause or inhibit inflammation. While it may be true that inflammatory molecules may be administered to patients, the mere finding of a positive result in the VPF assay would not be considered sufficient by one of skill in the art to warrant such use of the PRO326 polypeptide. Further, in the express absence of any showing that PRO326 is made *in vivo* as a component of an inflammatory response, no person of ordinary skill in the art would consider it more likely than not that antibodies against PRO3226 could be used to inhibit such a response. Therefore, the assertion that PRO326 would have a "real world" use based upon the positive result of the VPF assay is not substantial.

More particularly, PRO326 meets the specific criteria (A) and (B), as quoted from the MPEP, above. Based upon the disclosure in the specification as filed, the result of the VPF would motivate one of skill in the art to perform further basic research of the type disclosed by Rampart et al. to study the properties of PRO326 and determine *if* it *does* actually function as a pro-inflammatory molecule *in vivo*, experimentation that would be absolutely *required* by any medical institution prior to administering it to any patient for any reason. As PRO326 has not been associated with any *in vivo* inflammatory response, the assertion that antibodies to PRO326 can be used to inhibit such responses constitutes an assertion of a method of treating an unspecified disease or condition, as there is no disease or condition that has been shown to be associated with the presence or absence of PRO326 *in vivo*.

At p. 15 of the Brief, Appellants argue that PRO326 is not merely an irritant. Specifically, Appellants point to the examiner's statement in the February 4, 2005 Office Action that PRO326 polypeptides induce inflammation in an animal model, and that the results *might* indicate that PRO326 is an inflammatory cytokine. Appellants urge that the skilled artisan would consider it more likely than not that the PRO326 polypeptides are able to induce inflammation; and thus can be used to induce inflammation when desired or to make antibodies that inhibit inflammation when desired. This has been fully considered but is not found to be persuasive. An animal often experiences an inflammatory response when a foreign substance is introduced into the body, whether by injury or infection or ingestion, etc. However, the skilled artisan would not use just any foreign substance to induce inflammation without further research to determine exactly what sort and what magnitude of immune response is generated. Also, the assay provides no information regarding which inflammatory diseases, if any, involve PRO326.

From p. 15 to p. 16 of the Brief, Appellants urge that the examiner's arguments regarding a potential allergic reaction to PRO326 do not negate utility. Appellants argue that it is more likely than not that guinea pigs are not allergic to PRO326, since an allergic reaction would have required that the guinea pigs had been pre-exposed to PRO326. Appellants also urge that, even if the guinea pigs had experienced an allergic reaction to the PRO326, such would still demonstrate utility of the PRO326 polypeptides, since they induced an inflammatory response. Appellants conclude that the PRO326 polypeptides could be used to induce inflammation, and that PRO326 antibodies could be used to suppress an allergic response to PRO326. This has been fully considered but is not found to be persuasive. First, the guinea pigs would have had to have been previously exposed to a substance that shared an epitope with PRO326, and need not have been exposed to PRO326 *per se.* For example, people who are allergic to penicillin are generally allergic to all antibiotics of that class, even when the structures are not identical. Also, there is no evidence of record that skilled artisans (e.g., physicians) use allergens to induce a desired inflammatory response (e.g., such as for an infected, recalcitrant leg ulceration). The examiner's previous mention of a possible allergic response was made to illustrate that a positive result in the SVP assay does not indicate that it is more likely than not that the tested molecule is a pro-inflammatory cytokine. A positive result in the SVP assay can indicate that the tested molecule is a pro-inflammatory cytokine OR an allergen OR an irritant OR a toxin, etc. The art shows that the skilled artisan does not rely on a positive result in the assay alone to conclude that a molecule plays a role in inflammation. See Rampart et al., for example.

At p. 16 of the Brief, Appellants take issue with the examiner's characterization of the Hirahara et al. reference (cited in the Fong declaration) as not being comparable to those of the instant application since PRO326 tested positive in the assay whereas FXIII tested negative. Appellants argue that the specification and Hirahara et al. constitute evidence that both positive and negative results in the SVP assay establish utility as pro-inflammatory molecules and anti-inflammatory molecules, respectively. This has been fully considered but is not found to be persuasive. PRO326 did not test negative in the assay. Therefore, whether or not a molecule testing negative in the assay establishes a utility is off-point.

Beginning at page 17, appellants argue that the asserted utility need not be understood nor superior to other methods of attaining that utility. At pp. 17-18 of the Brief, Appellants take

issue with the examiner's statement that a positive result in the SVP assay is merely a jumping-off point, or an invitation to further experiment to determine the properties of PRO326. Appellants argue that a positive result in the SVP assay indicates induction of inflammation, and that the skilled artisan would have believed it more likely than not that the PRO326 polypeptides were useful for their asserted utility (as pro-inflammatory molecules). This has been fully considered but is not found to be persuasive. The disclosed SVP assay did not report results compared to controls, and indicated that even a "minimal perivascular infiltrate at the injection site is scored as positive." The identity of the cells types at the injection site was not disclosed. Clearly, the disclosed results are preliminary, and significant further research would be required from the skilled artisan to determine what type of immune response is induced by PRO326, and if it is any more significant than the immune response generated by an irritant or toxin. Further, the Examiner has repeatedly asserted that merely identifying an agent as a proinflammatory agent does not confer utility. It is not a real world use in the sense of 35 U.S.C. §101, as no one would administer this compound for the purpose of causing inflammation, based upon the results in the specification as filed. The only reason that this compound would be administered, based upon the results in the specification, would be for the purpose of further characterizing the response to the molecule, as was done by Rampart. Only *after* the results of such further experimentation were known would one be able to conceive of under what circumstances and for what purpose one would desire to cause inflammation by administering PRO326. That further experimentation is part of the inventive process.

At p. 18 of the Brief, Appellants argue that the examiner inappropriately focuses on the underlying mechanism resulting in positive results in the SVP assay, and that there is no legal requirement for a specification to disclose a mechanism. Appellants also urge that the examiner is inappropriately concerned with the magnitude of the immune response. This has been fully considered but is not found to be persuasive. While it is true that a specification need not disclose a mechanism, a specification must teach the skilled artisan how to make and use a claimed invention in its full scope without requiring undue experimentation. In the instant case, the disclosed SVP assay and results are so devoid of detail that it amounts to an invitation to experiment with PRO326 to determine its significance and how it can be used.

The Examiner has made no requirement that the mechanism by which the invention works be elucidated. Rather, the rejection under 35 U.S.C. §101 is on the basis that a mere showing that a compound has a positive response in the skin vascular permeability is not probative of any real world use for the compound. *If, in arguendo,* appellants had responded to the rejection by showing any example in which any compound that is characterized solely on the basis of a positive assay result in the skin vascular permeability assay was used for any real world use, the rejection would have been overcome. However, appellants have provided no such evidence, nor even any clear indication of why one would use a compound to cause inflammation. While it may be true that it would be desirable to stimulate particular subsets of immune cells under different conditions, the artisan would want to know what cells were stimulated by a particular compound before doing so, as evidenced by Rampart, for example. To use PRO326 polypeptides as urged by appellants to stimulate immune cells already at, and to induce migration of immune cells to, the site of infection, is purely speculative, as we simply don't know what *types* of cells are stimulated by PRO326- no characterization of the response was done, as was done by Rampart.

At pages 18-20 of the Brief, Appellants argue that the PRO326 polypeptides to which the claimed antibodies bind induce an inflammatory response in the SVP assay, allegedly establishing a patentable utility for PRO326 polypeptides based on their ability to induce inflammation. Appellants characterize SVP as a dye-based pro-inflammatory cell infiltration assay in skin in which PRO326 induces mononuclear cell, eosinophil, and PMN infiltration into the site of injection. This has been fully considered but is not found to be persuasive. Example 77 (Assay 64), the SVP assay, appears at pp. 210-211 of the specification and reads as follows:

> This assay shows that certain polypeptides of the invention stimulate an immune response and induce inflammation by inducing mononuclear cell, eosinophil and PMN infiltration at the site of injection of the animal. Compounds which stimulate an immune response are useful therapeutically where stimulation of an immune response is beneficial. This skin vascular permeability assay is conducted as follows. Hairless guinea pigs weighing 350 grams or more are anesthetised with ketamine (75-80 mg/Kg) and 5 mg/Kg xylazine intramuscularly (lM). A sample of purified polypeptide of the invention or a conditioned media test sample is injected intradermally onto the backs of the test animals with 100 µl per injection site. It is possible to have about 10-30, preferably about 16-24,

> injection sites per animal. One µl of Evans blue dye (1 % in physiologic buffered saline) is injected intracardially. Blemishes at the injection sites are then measured (mm diameter) at 1 hr and 6 hr post injection. Animals were sacrificed at 6 hrs after injection. Each skin injection site is biopsied and fixed in formalin. The skins are then prepared for histopathologic evaluation. Each site is evaluated for inflammatory cell infiltration into the skin. Sites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells may be neutrophilic, eosinophilic, monocytic or lymphocytic. At least a minimal perivascular infiltrate at the injection site is scored as positive, no infiltrate at the site of injection is scored as negative.

Contrary to Appellants' statements, the specification does not show that PRO326 induces mononuclear cell, eosinophil, and PMN infiltration into the site of injection. Rather, since PRO326 tested positive in the assay, the specification indicates that PRO326 injection yielded "visible inflammatory cell infiltration into the skin" and "[a]t least a minimal perivascular infiltrate at the injection site." The inflammatory cells may be "neutrophilic, eosinophilic, monocytic or lymphocytic." There was no disclosure of *which* inflammatory cells were at the site, and how the PRO326 injection site compared to controls in terms of magnitude of immune response or types of immune cells recruited, or any other details. Again, injection of lye, poison ivy extract, bee venom, or even a splinter would have yielded a positive result in this assay as disclosed.

At pages 20-21, Appellants allege that the art recognizes that the SVP assay is an *in vitro* assay useful for identifying compounds with inflammatory activity in vivo. Appellants argue that the SVP assay has been widely accepted in the art. Appellants rely upon Rampart et al. as allegedly using a rabbit skin neutrophil accumulation assay similar to the instant SVP assay to identify IL-8. Appellants state that, under pro-inflammatory conditions, several mechanisms act synergistically to mediate an increase in neutrophil accumulation, plasma extravasation, etc. Appellants argue that such events occur, for example, during the acute phase of an inflammatory response to a microbial stimulus or during pathologic conditions like graft rejection, edema, psoriasis, arthritis, tissue injury, etc. Appellants characterize Rampart et al. as suggesting the involvement of endogenous IL-8 in an acute phase inflammatory response of an animal to a microbial stimulus, and further disclosing suggestive data supporting its involvement in psoriasis

(at p. 24, col. 1, last paragraph). Appellants reason that *subsequent data* affirmed the involvement in IL-8 in several inflammatory conditions and in immune response, e.g., rheumatoid arthritis, asthma, leprosy, inflammatory bowel disease, atherosclerosis, cystic fibrosis, and respiratory syndromes. This has been fully considered but is not found to be persuasive. Rampart et al. found that IL-8 induced plasma leakage and neutrophil accumulation in rabbit skin (title). Rampart et al. specifically determined the type of immune cells that were recruited (neutrophils). The instant specification does not report what type(s) of immune cells were recruited by PRO326. Also, Rampart et al. did not merely assay the types of cells attracted, but also looked at the kinetics of the reaction, and concluded that based upon the *kinetics* of the responses, which were similar to those induced by C5a and FMLP, that "IL-8, if produced endogenously, may be involved in the acute phase of an inflammatory response to a microbial stimulus". Such is a speculative conclusion, and clearly would indicate to the person of ordinary skill in the art that the authors envisioned that substantial further work would have been required to confirm that speculation. In this specific case, human PRO326 was found to be an irritant to guinea pigs. Such *might* indicate that PRO326 is an inflammatory cytokine (although based on such a result, the person of ordinary skill in the art would not consider that to be a supportable conclusion), or alternatively it might indicate that the guinea pigs are allergic to PRO326, e.g. that the human PRO326 protein has an epitope that the guinea pigs were pre-sensitized to, or that the guinea pigs' bodies recognized PRO326 as a foreign substance, irritant, or toxin. In either case, as was the case in the Rampart et al. publication, the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of PRO326. Accordingly, it remains that the only inflammation that could be treated using anti-PRO326 agents at the time the invention was made is that actually caused by PRO326, which is a circular exercise with no meaning, as there is no reason to believe that any patient has any condition resulting from excess PRO326 based upon the results in the specification as originally filed. It remains that the skin vascular permeability assay does not give sufficient information so as to inform one of skill in the art as to how to use the polypeptides to which the claimed antibodies bind.

At page 14, and again at pages 21-24 of the brief, applicants refer to the Fong declaration. This declaration was previously considered, to the following effect:

In the declaration, items 1-9, Dr. Fong states that Assay # 64 is known as the Miles assay and is well known in the art as an assay to identify proinflammatory molecules. Declarant states that proinflammatory molecules can directly or indirectly cause vascular permeability by causing immune cells to exit from the blood stream and move to the site of injury or infection. Declarant states that these proinflammatory molecules recruit cells like leukocytes which includes monocytes, macrophages, basophils, and eosinophils. Declarant states that these cells secrete a range of cytokines which further recruit and activate other inflammatory cells to the site of injury or infection. Declarant states that these processes are critical and tightly regulated via diapedesis and extravasation steps. Declarant concludes that proinflammatory molecules are useful in treating infections, as local administration of the proinflammatory polypeptide would stimulate immune cells already present at the site of infection and induce more immune cells to migrate to the site, thus removing infection at a faster rate. Declarant points to MCP-1 and MCP-2 as being useful to cause neutrophils to extravasate, other CXC chemokines as being useful to activate neutrophils, and other CXC chemokines as being useful to cause chemotaxis of T lymphocytes. Declarant states that inhibitors of proinflammatory molecules are useful to treat diseases characterized by abnormal immune cell response. Declarant states that proinflammatory molecules with angiostatic properties are useful in treating tumors. Declarant states that the Miles assay was initially developed when researching the effect of histamine on the vascular system. Declarant states that subsequent workers have developed the assay into a quantitative one. This has been fully considered but is not found to be sufficient to overcome the rejection. The Miles assay is useful as a preliminary screen for potential proinflammatory molecules. Basic irritants, such as lye, would test positive in the Miles assay. Further work must be done subsequent to a positive result in a Miles assay to determine if and how a molecule may be useful as a proinflammatory. For example, MCP-1 and MCP-2 are not only positive in the Miles assay, they were also shown to have the specific activity of causing the extravasation of

neutrophils. As Declarant points out, other CXC cytokines, while scoring positive in a Miles assay, have subsequently been shown to have specific activities of activating neutrophils or being chemotactic for T lymphocytes. The state of the art shows that a positive result in the Miles assay is insufficient for the skilled artisan to conclude that a molecule is a proinflammatory molecule with specific activities, as opposed to a basic irritant. While particular irritants may have uses that stem from that irritant capability, in the absence of further characterization of what type of reaction the substance causes and what the systemic effects of such are, the result remains a preliminary one, necessitating substantial further research to determine how to use the compound. For example, the Rampart reference (Am. J. Pathol. 135:21, 1989) is one in which IL-8 was found to induce plasma leakage and neutrophil accumulation in rabbit skin (title). Rampart et al. did not merely assay the types of cells attracted, but also looked at the kinetics of the reaction, and concluded that based upon the *kinetics* of the responses, which were similar to those induced by C5a and FMLP, that "IL-8, if produced endogenously, may be involved in the acute phase of an inflammatory response to a microbial stimulus". Such is a speculative conclusion, and clearly would indicate to the person of ordinary skill in the art that the authors envisioned that substantial further work would have been required to confirm that speculation.

In point 10, Declarant states that the skin vascular permeability assay was used to determine if blood coagulation factor XIII (FXIII) could be used in treating Shonlein Henoch Purpura (SHP). Declarant refers to Hirahara et al. (1993, Thrombosis Res. 71:139-148) as showing that FXIII stabilized microvasculature, leading to less permeability, and therefore may be useful in treatment of SHP. This has been fully considered but is not found to be sufficient to overcome the rejection. In the instant case, the PRO326 protein tested positive in the assay. FXIII tested negative. Therefore, the results are not comparable.

In point 11, Declarant states that the Miles assay was used by Senger et al. (1983, Science 219:983-985) to show that a secreted factor called VPF caused vascular permeability. This has been fully considered but is not found to be sufficient to overcome the rejection. Senger et al. set out to determine why vessels lining the peritoneal cavities of rodents

with ascites tumors display markedly greater permeability than vessels in control animals. Senger et al. only conclude that secretion of permeability-increasing activity appears to be a common feature of tumor cells and that VPR has permeability-increasing activity. Senger et al. do not suggest that VPR can be considered a pro-inflammatory molecule useful for treatment of injury or infection.

In point 12, Declarant states that Yeo et al. (1992, Clin. Chem. 38:71-75) confirmed the viability of the skin vascular permeability assay by correlating it with disassociation enhanced lanthanide fluoroimmunoassay (DELFIA) results. Declarant states that VPF (VEGF) tested positive in the skin vascular permeability assay and then anti-VPF antibodies were used to quantify the amount of VPF in the DELFIA. Declarant states that the DELFIA assay has greater sensitivity. This has been fully considered but is not found to be sufficient to overcome the rejection. Yeo et al. do not assert that the DEFLIA assay or the Miles assay can be used to identify proinflammatory molecules that can be used to treat injury or infection. Yeo et al. disclose that VPF may be the same protein as VEGF, which has been shown to be a mitogen specific for endothelial cells, and may promote tumor angiogenesis via its mitogenic activity for endothelial cells. However, the specific and useful activity of VEGF as an angiogenic factor was not identified by the Miles assay or the DEFLIA assay. Significant further research had to be conducted to identify this specific and substantial activity.

In point 13, Declarant reviews the skin vascular permeability assay and refers to Exhibit I as showing a positive reaction for a PRO polypeptide. This has been fully considered but is not found to be sufficient to overcome the rejection. It is not clear that the PRO polypeptide shown in the exhibit is the same PRO polypeptide of the instant claims. Furthermore, the assay does not provide the skilled artisan with the guidance necessary for the skilled artisan to determine how to use the PRO polypeptide without resorting to undue experimentation.

In point 14, Declarant provides his expert opinion that the PRO polypeptide that shows activity in the skin permeability assay has specific, substantial and credible utilities. Declarant states that the application discloses that the results of the skin permeability assay were further analyzed by histopathological examination to rule out inflammation

due to endothelial cell damage or mast cell degranulation. Declarant concludes that the vascular permeability observed was not due to histamine release or endothelial cell damage. Declarant asserts that the PRO polypeptides testing positive in the assay are useful to enhance immune cell recruitment to sites of injury or infection, or inhibitors to treat autoimmune diseases. Declarant further states that angiogenic or angiostatic properties of proinflammatory would find utility in controlling tumorigenesis. This has been fully considered but is not found to be sufficient to overcome the rejection. The specification describes analysis of the results of the skin vascular permeability assay as follows:

> The skins are then prepared for histopathologic evaluation. Each site is evaluated for inflammatory cell infiltration into the skin. Sites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells may be neutrophilic, eosinophilic, monocytic or lymphocytic. At least a minimal perivascular infiltrate at the injection site is scored as positive, no infiltrate at the site of injection is scored as negative.

As this quotation shows, the Declarant is not entirely correct with respect to the facts. The PRO polypeptides used in the assay are not further analyzed by histopathological examination **to rule out inflammation due to endothelial cell damage or mast cell degranulation**. In this specific case, human PRO326 was found to be an irritant to guinea pigs. Such *might* indicate that PRO326 is an inflammatory cytokine (although based on such a result, the person of ordinary skill in the art would not consider that to be a supportable conclusion), or alternatively it might indicate that the guinea pigs are allergic to PRO326, e.g. that the human PRO326 protein has an epitope that the guinea pigs were pre-sensitized to. In either case, as was the case in the Rampart et al. publication, the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of PRO326. Accordingly, the only inflammation that could be treated using anti-PRO326 agents at the time the invention was made is that actually caused by PRO326, which is a circular exercise with no meaning (as there is no reason to believe that any patient has any condition resulting from excess PRO326 based upon the results in the specification as originally filed). It remains

that the skin vascular permeability assay does not give sufficient information so as to inform one of skill in the art as to how to use the polypeptides. Finally, Declarant's comments regarding angiogenic or angiostatic activities of the PRO polypeptides is off-point, since these activities were not disclosed in the specification. Finally, it is noted that opinion declarations are evaluated for the reasonableness and validity of the opinion; however, no weight is given to an opinion on the ultimate legal conclusion in issue.

At page 20-21, appellants argue that the art recognizes that the SVP assay is useful for identifying compounds with inflammatory activity. This is true, but it is a partial truth. By appellants own admission in the Brief, Ramparts findings "*were correlated with albumin flux and neutrophil dependent edema in skin.*" No such correlation was shown for PRO326. The other assertions in point 9 of the Fong declaration have been addressed above. The Examiner does not question that similar assays are used in the art. What is in question is that there are *no* reported cases in which the biological activity of a molecule was concluded on the basis of a single such assay and in the express absence of any characterization of the cellular or cytokine response induced by the protein.

At page 21, appellants argue that the SVP assay results determined that PRO326 polypeptides have inflammatory activity *in vivo*. This is a very important point, and one that is being over-simplified by appellants. What *has* been shown by the single assay in question is that if one injects the back of a hairless guinea pig with a solution comprising PRO326, some kind of inflammatory response will ensue. What has *not* been shown is: It has *not* been shown *if* PRO326 is produced *by* the guinea pig, nor under what conditions. It has *not* been shown what types of cells may have migrated to the wound response, a characterization that is shown to be standard in the art when using such an assay. It has *not* been shown that the expression profile of PRO326 is similar to any other protein (as was done by Rampart, in attributing activity to IL-8). Hence, appellants own argument shows how very preliminary the result is, and that substantial further experimentation would be required to determine a utility for PRO326. With respect to the use of anti-PRO326 as anti-inflammatory compounds, one would first have to show that

PRO326 is *produced* as part of an inflammatory response *in vivo* for such to constitute a substantial assertion. That has not been done.

Appellants arguments at pages 21-22 are reiterative of earlier arguments and have been fully addressed, above.

At page 23-34, appellants imply that the Examiner has failed to consider the totality of evidence, and must consider opinions. The totality of evidence has been considered. With regard to the Fong declaration, the opinions were considered, but in light of the *facts* of the case and the *facts* of the cited art, were not found to be persuasive (see above). The totality of the record including the assay in the specification, the Fong declaration, and the various reference cited by appellants, supports the Examiner's position that there is no readily available, real world use for PRO326, and that all that the specification enables is further experimentation to characterize the properties of the encoded protein.

It is not the robustness nor the versatility of the SVP assay that are at issue here. The assay shows that inflammation resulted when guinea pigs were injected with PRO326. However, the totality of the evidence of record shows that that sole result would not be considered by the skilled artisan to support as **substantial** an assertion that PRO326 is a pro-inflammatory molecule *in vivo* , nor does it lead to any readily available, real world use for PRO326.

In summary, the rejection under 35 U.S.C. §101 is made on the basis that the skin vascular permeability assay upon which appellants reply merely demonstrates that PRO326 is an irritant. The prior art, as evidenced by Rampart, for example, evinces that one of skill in the art would *not* conclude PRO326 to be useful as a pro-inflammatory molecule on the basis of the single assay disclosed in the specification, but rather would have to perform substantial further experimentation to determine *what types* of cells were affected, and/or whether there are other cytokines that are induced by PRO326, and if so which, before determining how to use the protein bound by the claimed antibodies. In the absence of such further information, all that is provided by the specification is the isolation of a nucleic acid from humans and the germ of an idea that the protein encoded to which the claimed antibodies bind may someday be shown to be a biologically interesting or important molecule. The issue here is *not*, as repeatedly characterized by appellants whether the Examiner's grounds of rejection is sufficient to "negate their utility" as stated at page 14 of the brief, but rather that the specification as originally filed

fails to present a specific, substantial and credible assertion of a real world use for the claimed antibodies as required by 35 U.S.C. §101 and as interpreted in the Utility Guidelines found in the MPEP.

Applicants arguments at page 26 do not pertain to any ground of rejection under appeal. The rejection under 35 U.S.C. §112, first paragraph is based entirely on the lack of utility. Accordingly, no response is necessary to the additional arguments.

Arguments pertaining to art rejections:

Regarding the rejection over Wu et al., appellant argues at page 27-28 that the antibodies of Wu would not be considered to specifically bind to the protein of SEQ ID NO: 294. This argument has been fully considered but is not deemed persuasive. Wu's protein shares numerous regions of absolute identity to SEQ ID NO: 294, such that a large number of antibodies to Wu's protein would recognize the same protein sequence, be it in Wu's protein or SEQ ID NO: 294. As used in the art, 'specific' is not necessarily synonymous with 'binds exclusively to' as urged by applicants. Rather, specificity is relative, such that antibodies 'specific' for one protein can bind to another protein with similar sequence. For example, antibodies specific to PDGF have, indeed, been described as binding to CTGF, as evidenced by U.S. Patent Number 5,783,187. Accordingly, antibodies to Wu's protein that also bind to the same epitopic structure of SEQ ID NO: 294 would be considered to be "specific", and the antibodies of Wu anticipate the claims.

Regarding the rejection over Wang et al., appellant's argument that Wang is not applicable as prior art is deemed not persuasive. Based upon the lack of utility and enablement of the claimed subject matter, priority is granted only to the instant filing date, 7/17/01.

Regarding the rejections under 35 U.S.C. §102(a), appellants argue at page 29 that (a) they deserve a priority date earlier than Nagase and Kawai, and (b) that an antibody to Suzuki's protein would not be "specific" for the protein of SEQ ID NO: 294. With regard to the former

argument, see the paragraph immediately above. With regard to the latter, see the discussion of the rejection over Wu et al., two paragraphs above. Due to numerous stretches of identity between SEQ ID NO: 294 and Suzuki's protein, antibodies raised against the latter would be expected to specifically bind to the former.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the Examiner in the Related Appeals and Interferences section of this Examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Should Appellants request an oral hearing, the Examiner requests to be present and to present arguments.

Respectfully submitted,

Lorraine Spector
Primary Examiner

Conferees:

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER